Docket No. 1919/60390-AZ-PCT-US/JPW/GJG/ML

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Arlindo Castelhano, et al.

Serial No. : 10/816,329 Group Art Unit: 1624

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Title : PYRROLO[2,3d]PYRIMIDINE COMPOSITIONS AND THEIR USE

1185 Avenue of the Americas
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March 19, 2008

MAIL STOP RCE
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Sir:

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

This Information Disclosure Statement is being submitted with a Request for Continued Examination ("RCE") in connection with the above-identified patent application.

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants would like to direct the Examiner's attention to the following references, which are listed on Form PTO-1449 **(Exhibit A)**.

Reference items 39, 40 and 78 were cited in the subject application by the Examiner. Therefore, copies of these documents are not provided.

In addition, reference items 1-11 are either U.S. patents or U.S. patent application publications. Pursuant to 37 C.F.R. 1.98(a)(2), copies of references 1-11 are not being submitted.

Furthermore, copies of the documents listed herein as items 14-18 are not provided because these Hungarian Patents correspond to either WIPO publications or European patents, copies of which are included herein already.

Copies of the documents listed herein as items 12, 13, 19-38 and 41-77 are attached hereto as **Exhibits 1-59**.

1. U.S. Patent No. 5,889,026, issued March 30, 1999, Alanine et al.;

2. U.S. Patent No. 6,117,878, issued September 12, 2000 to Linden, J.;

3. U.S. Patent No. 6,465,456, issued October 15, 2002, Springer et al.;

4. U.S. Patent No. 6,680,322, issued January 20, 2004 to Castelhano, A. et al.;

5. U.S. Patent No. 6,916,804, issued July 12, 2005 to Castelhano, A. et al.;

6. U.S. Patent No. 7,202,252, issued April 10, 2007, Wilson et al.;

7. U.S. Patent Application Publication No. 2003-0139427 A1, published November 1, 2005 (U.S. Serial No. 10/227,378, filed August 23, 2002) (Castelhano, A. et al.);

8. U.S. Patent Application Publication No. 2003-0229067 A1, published December 11, 2003 (U.S. Serial No. 10/326,005, filed December 20, 2002) (Castelhano, A. et al.);

9. U.S. Patent Application Publication No. 2004-0082598 A1, published April 29, 2004 (U.S. Serial No. 10/718,280, filed November 20,2003) (Castelhano, A. et al.);

10. U.S. Patent Application Publication No. 2004-0082599 A1, published April 29, 2004 (U.S. Serial No. 10/718,411, filed November 20,2003) (Castelhano, A. et al.);

11. U.S. Patent Application Publication No. 2005-0119271 A1, published June 2, 2005 (U.S. Serial No. 10/995,239, filed November 18, 2004) (Castelhano, A. et al.);

12. U.S. Patent Application Serial No. 10/010,092, filed November 30 2001 (Castelhano, A. et al.) **(Exhibit 1)**;

13. European Patent No. EP 1246623 B1, published August 9, 2006 **(Exhibit 2)**;

14. Hungarian Patent No. HU P9303515 (corresponds to WO 94/13676);

15. Hungarian Patent No. HU P9501230 (corresponds to EP 0682027);

16. Hungarian Patent No. HU P9602016 (corresponds to WO 95/19970);

17. Hungarian Patent No. HU P9402829 (corresponds to WO 93/20078);

18. Hungarian Patent No. HU P9602017 (corresponds to WO 95/19774);

19. PCT International Application No. WO 2001/039777, published June 7, 2001 (Castelhano, A. et al.) **(Exhibit 3)**;

20. PCT International Application No. WO 2002/057267, published July 25, 2002 (Castelhano, A. et al.) **(Exhibit 4)**;

21. PCT International Application No. WO 2003/048120, published June 12, 2003 (Castelhano, A. et al.) **(Exhibit 5)**;

22. PCT International Application No. WO 2003/053361, published July 3, 2003 (Castelhano, A. et al.) **(Exhibit 6)**;

23. PCT International Application No. WO 2003/053366, published July 3, 2003 (Castelhano, A. et al.) **(Exhibit 7)**;

24. PCT International Application No. WO 97/47601, published December 18, 1997 **(Exhibit 8)**;

25. PCT International Application No. WO 99/64407, published December 16, 1999 **(Exhibit 9)**;

26. PCT International Search Report issued in PCT International Application No. PCT/US2001/045280, filed November 30, 2001 **(Exhibit 10)**;

27. PCT International Search Report issued in PCT International Application No. PCT/US2002/38055, filed November 27, 2002 **(Exhibit 11)**;

28. PCT International Search Report issued in PCT International Application No. PCT/US2002/40890, filed December 20, 2002 **(Exhibit 12)**;

29. PCT International Search Report issued in PCT International Application No. PCT/US2002/41273, filed December 20, 2002 **(Exhibit 13)**;

30. PCT International Preliminary Examination Report issued in PCT International Application No. PCT/US2001/045280, filed November 30, 2001 **(Exhibit 14)**;

31. PCT International Preliminary Examination Report issued in PCT International Application No. PCT/US200/38055, filed November 27, 2002 **(Exhibit 15)**;

32. PCT International Preliminary Examination Report issued in PCT International Application No. PCT/US2002/40890, filed December 20, 2002 **(Exhibit 16)**;

33. PCT International Preliminary Examination Report issued in PCT International Application No. PCT/US2002/41273, filed December 20, 2002 **(Exhibit 17)**;

34. Partial European Search Report for EP Application No. 01 99 7029; completed 12/21/2004 **(Exhibit 18)**;

35. Partial European Search Report for EP Application No. 06 01 6543.8; completed 10/4/2006 **(Exhibit 19)**;

36. Supplementary European Search Report for EP 02 80 5676; issued 2/7/2005 **(Exhibit 20)**;

37. Baraldi, P.G. et al., (1999) "A1 and A3 adenosine receptor agonists: an overview." *Expert Opinion on Therapeutic Patents*, 9(5):515-527 **(Exhibit 21)**;

38. Baraldi P.G. (2003) "Recent developments in the field of A2A and A3 adenosine receptor antagonists" Eur. J. Med. Chem. 38(4) 367 **(Exhibit 22, abstract only)**;

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40. Baraldi, P.G. et al., (2004) "Allosteric modulators for the A1 adenosine receptor." *Expert Opinion on Therapeutic Patents*, 14(1):71-79;

41. Borman, S. (2001) "A3 Receptors" C&EN, 79(7), 37 **(Exhibit 23)**;

42. Bremer et al. (2002) "Therapy of Crohn's Disease in Childhood", Expert Opin. Pharmacother. 3(7): 809-825 **(Exhibit 24)**;

43. Christofi, F.L. et al. (2001), "Differential Gene Expression of Adenosine A1, A2a, A2b, and A3 Receptors in the Human Enteric Nervous System", J. Comp. Neurol. 439(1): 46-64 **(Exhibit 25)**;

44. Corset, V. et al. (2000), "Netrin-1-mediated axon outgrowth and cAMP production requires interaction with adenosine A2b receptor", Nature, 407 (6805): 747-750 **(Exhibit 26)**;

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48. Feoktistov, I. et al., (2002) "Differential Expression of Adenosine Receptors in Human Endothelial Cells", Circulation Research 90: 531-538 **(Exhibit 30)**;

49. Fishman P (2003) "Pharmacology and therapeutic applications of A3 receptor subtype" Curr. Top. Med. Chem. 3(4): 463-9 **(Exhibit 31)**;

50. Gao, Z. et al., "A_{2B} Adenosine and $P2Y_2$ Receptors Stimulate

Mitogen-activated Protein Kinase in Human Embryonic Kidney-293 Cells" *J. Bio. Chem.* (1999) 274(9): 5972-5980 **(Exhibit 32)**;

51. Grant, M.B. et al., (2001) "Proliferation, Migration, and ERK Activation in Human Retinal Endothelial Cells through A_{2B} Adenosine Receptor Stimulation", Invest. Opthalmol. Vis. Sci. 42(9): 2068-2073 **(Exhibit 33)**;

52. Guo, Y. et al., (2001) "Targeted deletion of A3 adenosine receptor confers resistance to myocardial ischemic injury and does not prevent early preconditioning." *J Mol Cell Cardiol*, 33:825-830 **(Exhibit 34)**;

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55. Hoeschst India Ltd., India "Pharmacologically active pyrimido "[4,5-b]indoles and their salts." Database accession No. 106:84629 HCA XP002121648 **(Exhibit 37)**;

56. Kiichiro, K. et al. "Synthesis of pyrazinecarboxylic acid derivs. - (II) derivs. of 3-aminopyrazinecarboxylic acid"

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57. Kiritsy, J.A. et al., (1978) "Synthesis and Quantitative Structure-Activity Relationships of Some Antibacterial 3-Formylrifamycin SV N-(4-Substituted phenyl) piperazinoacethydrazones" J. Med. Chem. 21(12): 1301-1307 **(Exhibit 39)**;

58. Klumpp, D.A. et al., (1999) "Synthesis of Aryl-Substituted Piperidines by Superacid Activation of Piperidones" J. Org. Chem. 64(18): 6702-6705 **(Exhibit 40)**;

59. Linden, J. et al., (1998) "The Structure and Function of A1 and A2B Adenosine Receptors" Life Sciences 62(17-18): 1519-1524 **(Exhibit 41)**;

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(Exhibit 45);

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68. Polosa (2002) "Adenosine-receptor subtypes: their relevance to adenosine-mediated responses in asthma and chronic obstructive pulmonary disease", Eur. Respir. Journal 20,488-496 **(Exhibit 50)**;

69. Priego, E.-M. et al., "Pyrido[2,1-*f*]purine-2,4-dione Derivatives as a Novel Class of Highly Potent Human A_3 Adenosine Receptor Antagonists", (2002) J. Med. Chem., 45(16): 3337-3344 **(Exhibit 51)**;

70. Ralevic, V. And Burnstock, G., (1998) "Receptors for

Purines and Pyrimidines", Pharmacol. Rev. 50(3): 413-492 **(Exhibit 52)**;

71. Regnauld, K. et al., (2002) "G-protein αolf subunit promotes cellular invasion, survival, and neuroendocrine differentiation in digestive and urogenital epithelial cells", Oncogene 21(25): 4020-4031 **(Exhibit 53)**;

72. Robinson, "Medical Therapy of Inflammatory Bowel Disease for the 21st Century", Eur J Surg. Suppl 582:90-98, 1998 **(Exhibit 54)**;

73. Simone, Oncology: Introduction Cecil Textbook of Medicine, 20th Edition, Vol. 1, pp. 1004-1010, 1996 **(Exhibit 55)**;

74. Singh et al., "Immune therapy in inflammatory bowel disease and models of colitis", British Journal of Surgery, 88: 1558-1569, 2001 **(Exhibit 56)**;

75. Tanaka, H. et al.' "Preparation and formulation of fused pyrimidine compounds as CRF receptor antagonists." Database accession no. 129:109098 HCA XP002121647 **(Exhibit 57)**;

76. Van Niel, M.B. et al., "Fluorianation of 3-(3-(Piperidin-1-yl)propyl)indoles and 3-(3-(Piperazin-1-yl)propyl)indoles Gives Selective Human 5-Htid Receptor Ligands with Improved Pharmokinetic Profiles" J. Med. Chem. (1999) 42(12): 2087-2104 **(Exhibit 58)**;

77. West, R.A. et al. (1961) "2-alkyl(aryl)-and 2,7-dimethyl-4-

substituted aminopyrrolo[2,3—d]pyrimidines." *J. Org. Chem.*, 26:3809-3812 **(Exhibit 59)**; and

78. Yan, Luo et al., Expert Opinion on Emerging Drugs 2003,vol. 8, no. 2 pp. 537-576.

Applicants request that the Examiner review the references and make them of record in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any other fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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